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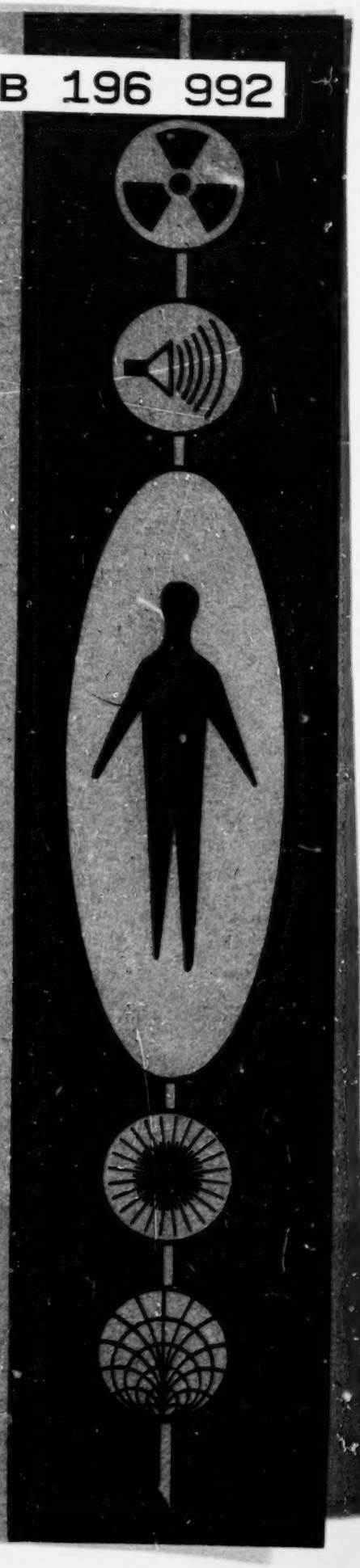
A Review of Radium Toxicity Studies



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DBE 70-5 A Review of Radium Toxicity Studies (December 1970)

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A Review of Radium Toxicity Studies

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December 1970

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Bureau of Radiological Health
Rockville, Maryland 20852

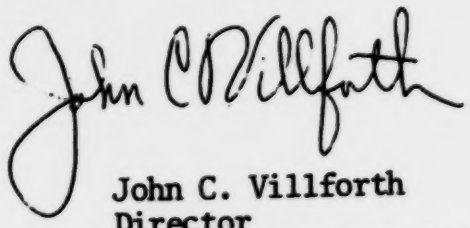
FOREWORD

The Bureau of Radiological Health conducts a national program to limit man's exposure to ionizing and nonionizing radiation. To this end, the Bureau (1) develops criteria and recommends standards for safe limits of radiation exposure, (2) develops methods and techniques for controlling radiation exposure, (3) plans and conducts research to determine health effects of radiation exposure, (4) provides technical assistance to agencies having radiological health programs, and (5) conducts an electronic product radiation control program to protect the public health and safety.

The Bureau publishes its findings monthly in Radiological Health Data and Reports, appropriate scientific journals, and from time to time in Division-sponsored technical reports.

The technical reports published by the Division of Biological Effects contain information generated by the Division staff which is timely and useful to the radiological health program. Subjects covered by these reports are varied, for the Division is charged with developing--through animal investigations and population studies--knowledge of the biological effects of radiation delivered to man from his environment and from his use of substances and devices that emit radiation. The reports are distributed to persons and repositories that have expressed an interest in the biological effects of radiation; in addition, the reports are available from the National Technical Information Service.

Readers are encouraged to report omissions or errors to the Bureau. Additional comments or requests for further information are also solicited.



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PREFACE

The Public Health Service has a responsibility to recognize public concern regarding exposure to ionizing radiation and its potential health effects. This responsibility includes a continuing evaluation of new sources of potential radiation injury and the review of information pertinent to recommendations, guidelines, and standards for radiation protection. One of the major efforts pertaining to the health effects of radiation has been the studies of humans exposed to radium. These radium toxicity studies are vitally important to our assessment of any health hazards because they represent a large body of information on radiation effects in humans upon which protection standards for many sources of radiation are based. The scientists who have conducted these studies have made significant contributions, requiring many years of effort, by providing excellent records with continuing interpretation and evaluation.

The International Commission on Radiological Protection (ICRP) and the Federal Radiation Council (FRC) have long advocated radiation protection standards based on the assumptions: 1) that the relationship between the biological effect and the amount of the radiation dose is linear without a threshold, and 2) that any radiation exposure may have an accompanying biological risk. Under these assumptions it has been possible to relate very low doses to assumed biological effects even though they may not be detectable. It has been generally agreed that any effects which may actually occur will not exceed the amount predicted under the first of these assumptions. Nevertheless, much concern exists today on the adequacy of our radiation standards, particularly in view of the fact that, perhaps for the first time in our history, large numbers of our population could be subject to exposure from ionizing radiation other than that used in the healing arts. This potential exposure arises primarily because of the need for electrical power and its availability through nuclear power plants. To assure confidence in the safety of nuclear facilities, periodic reevaluation of our protection standards is advisable. This report is not an evaluation of standards per se, but rather is a discussion of the important radium toxicity studies and the interpretation of these studies in regard to linearity of the dose-effect relationship and the existence of a threshold for radiation effects.

The Division of Biological Effects greatly appreciates the time and effort the following individuals have devoted to reviewing and

commenting on earlier drafts of this paper: R. D. Evans, A. J. Finkel, M. P. Finkel, R. J. Hasterlik, E. Landau, F. J. Massey, Jr., C. W. Mays, C. E. Miller, A. R. Tamplin, J. R. Totter, P. J. Walsh, and A. H. Wolff. Responsibility for errors of omission or commission, of course, are those of the authors alone.

The Public Health Service will continue to evaluate additional information as it becomes available. Further studies to combine the human radium data using common dosage parameters are either in progress or under consideration at several institutions in this country and abroad. These studies, when completed, will greatly improve our understanding of radium toxicity and add to our knowledge and understanding of the biological effects of ionizing radiation. In the meantime, we solicit the interest and comments of all who are concerned with these aspects of radiological health.

William A. Mills

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A REVIEW OF RADIUM TOXICITY STUDIES

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ABSTRACT

The debate concerning the linear or threshold response of somatic radiation injury has recently been focused on the human radium toxicity studies. Because of the critical public health significance of the data derived from these studies, a task group from the Division of Biological Effects of the Bureau of Radiological Health undertook a review of the available human and animal radium studies for the purpose of determining the extent to which animal and human data are sufficient to resolve the question of a dose-response relationship. The review contained in this report indicates that the animal and human radium experience to date is not sufficient to specify an unequivocal dose-response model. Therefore, in the low dose regions expected to be experienced by the general public, the assumption of a linear, non-threshold model continues to be a prudent public health philosophy for standards setting.

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INTRODUCTION

Recent publications (1-6) concerning the human radium experience have raised questions surrounding the linear and threshold hypotheses of somatic radiation damage. Because of the critical public health significance* of these questions, a task group from the Division of Biological Effects of the Bureau of Radiological Health was formed to analyze the current and pertinent human and animal radium toxicity studies. This report is intended to be an objective assessment of the published radium work to date. It is prepared as a report for the use of the Bureau of Radiological Health and does not pretent to provide any findings which are new or necessarily unique.

The human radium experience review concentrates on bone sarcomas, carcinomas of the paranasal sinuses and mastoids, and leukemia and blood dyscrasias in two closely followed American study groups: 1) the Massachusetts Institute of Technology (MIT) series (1,2), and 2) the Argonne National Laboratory (ANL) - Argonne Cancer Research Hospital (ACRH) series (3,4). Other studies will be noted but their importance to this analysis is lessened for various reasons which will be given.

Studies with animals exposed to radium, in which the principal endpoint is bone sarcoma, include: 1) the University of Utah beagle dog study (8,9), 2) the University of California at Davis beagle dog study (10), and 3) the Argonne National Laboratory mouse study (11). Other radium studies on animals predate those mentioned above. They were omitted from this analysis for various reasons, including inadequate statistical design, high dosages, small numbers, and early termination.

The importance and relevance of the studies reviewed herein are widely acknowledged. The human exposure problem is a very real one, and dedicated radiological health workers recognize their obligations to thoroughly investigate instances where humans have been inadvertently exposed to radiation. Meaningful animal experimentation is also necessary to supplement the human studies. Retrospective studies of accidentally exposed human populations commonly have deficiencies, however, that are characteristic of the data and beyond the control of the investigator. Animal studies, no matter how complete, possess the inherent difficulties of extrapolation between animal and human populations. This critique, in pointing out areas in the studies reviewed

*Radiation guidelines set by the ICRP and NCRP for boneseeking radionuclides, such as ^{239}Pu and ^{90}Sr, are based on the guidelines set for ^{226}Ra (2,7).

that do not allow acceptance of a dose-response model from these data, should not be construed to imply criticism of the techniques of the respective investigators.

DEFINITION OF TERMS

Part of the controversy between the proponents of the various dose-response models may arise from the ambiguity of the terms. For the purposes of this report, a linear model is any model in which the incidence of the given biological endpoint in a specified dose range varies proportionally with the dose delivered to the organism. This term should not be confused or equated to the term, non-threshold. A non-threshold model is any model (linear or other) in which the incidence increases monotonically as dose increases from zero to that dose region where effects from dose-related causes other than the endpoint of interest occur before the onset of the endpoint, concealing its recognition. A threshold model is any model (linear or other) in which the incidence is zero up to some positive threshold dose, at which point incidence begins to increase and continues to increase monotonically as dose increases throughout the remainder of the dose domain to that dose region where the endpoint is masked by other dose-related effects. Thus the term threshold implies the existence of a dose below which the incidence of the endpoint of interest is zero, and the term non-threshold denies the existence of such a dose. A linear model may be either threshold or non-threshold. Conversely, both threshold and non-threshold models can be either linear or non-linear.

HUMAN RADIUM STUDIES

Introduction

Five human radium toxicity groups are being studied: 1) the MIT series (1,2), 2) the ANL-ACRH series (3,4), 3) the New Jersey dial painters (12), 4) the English dial painters (13), and 5) the German "Peteosthor" patients (14,15). Most of the present information concerning dose-response relationships in the human radium experience is derived from the MIT and ANL-ACRH studies. The characterization of a dose-response function is not possible in the New Jersey (12) and English (13) dial painter studies because of insufficient numbers of studied individuals in the high dose groups, the large proportion of individuals in the very low dose groups (<0.01 μCi residual body burden ^{226}Ra), and the absence of tumors or other biological responses. Spiess (14) has given a breakdown of various clinical responses resulting from the intravenous administration of "Peteosthor", a preparation containing ^{224}Ra, but limitations in both followup and dosimetry and the lack of a dose-response analysis restrict the usefulness of the study to this review. The lowest quantities of ^{224}Ra for which a number of biological responses were observed is

stated, but the total amounts of radioactivity injected (μCi ^{224}Ra) are of a greater magnitude than those reported for the ^{226}Ra in the MIT and ANL-ACRH groups. Spiess and Mays (15) in a further analysis of the ^{224}Ra patients revised the dosimetry and developed a relationship between bone sarcoma incidence and skeletal dose in rads. The metabolism and retention of the short lived, surface seeking ^{224}Ra is so different from the long lived, volume seeking ^{226}Ra however, that the effects of the two nuclides are not readily combinable. For these reasons, the present review concentrates on the MIT (1,2) and ANL-ACRH (3,4) investigation, omitting other studies from further consideration.

Retention Functions

Prior to a discussion of the MIT and ANL-ACRH studies, a mention of radium retention models is necessary because of their importance in the dose and burden estimations in both studies. For radium retention, Norris et al. (16) have discussed two retention models: One describing the retention after a single injected burden and the other describing the retention after a continuous injected or ingested burden. The single injection model is a power function of the following form

$$R(t) = at^b, \; t \geq 1 \qquad (1)$$

where R(t) is the fraction of radionuclide retained in the body "t" days after injection, "a" is a constant representing the fraction retained after 1 day, and "b" is a constant related to the rate of disappearance of the radionuclide. The continuous injection or ingestion model is a modified power function given in altered form by A. Finkel et al. (3,4) as follows

$$R(t,F) = \frac{a}{b+1}[(t+F)^{b+1} - t^{b+1}], \; t \geq 0 \qquad (2)$$

where R(t,F) is the amount of radionuclide retained "t" days after cessation of administration, F is the time in days over which the radionuclide was administered, and "a" and "b" are the same constants as were described for the single injection model. The constants "a" and "b" are determined from the single injection model and are used in both the single injection and continuous administration functions. Two sets of estimates for "a" and "b" have been derived for man: Norris et al. (16) have determined a = 0.54 and b = -0.52 and Miller and Finkel (17) have estimated a = 0.30 and b = -0.44. These two sets of estimates cannot be statistically distinguished from one another because of the variation inherent in the estimation process. Therefore one must assume that either set of estimates can be used in Eq. (1) to describe radium retention in man.

The radon retention function is given by Norris et al. (16) and follows the power function of Eq. (1) with constants estimated by a = 0.021 and b = -0.28.

The MIT Study

The MIT series reported by Evans et al. (1,2) encompasses a closely followed group of radium dial painters, iatrogenic patients, and radium chemists who received body burdens of radium (^{226}Ra) and/or mesothorium (^{228}Ra) over a "brief exposure" time usually less than one year (1). Cumulative rads (CR) and cumulative rad year (CRY) skeletal average doses* were calculated from the measured current or terminal burdens for each reported individual. The doses were arranged in the following classes** (2):

Class	Dose Range (Cumulative Rads)
a	1 - 50
b	50 - 100
c	100 - 300
d	300 - 600
e	600 - 1,000
1	1,000 - 2,500
2	2,500 - 5,000
3	5,000 - 10,000
4	10,000 - 20,000
5	20,000 - 50,000

Two types of tumors were studied; carcinomas of the paranasal sinuses or mastoid processes and bone sarcomas. The two types of tumors were combined to compute a tumor incidence for each dose class. All self-selected*** cases, i.e., those that came to the attention of the investigators as a result of the discovery of symptoms of radiogenic injury, were omitted from the statistical analyses of the incidence data.

There are several important dose-response considerations evident in the Evans et al. (1,2) analysis of the MIT data. Among these are some strong points as well as some limitations which are discussed below. Many of these limitations are not peculiar to the Evans et al. (1,2) analysis, but are inherent in the epidemiologic treatment of human data.

First there is the problem of dosimetry. Evans et al. (1,2) recognize that the representation of dose by a single quantity has many shortcomings, including its failure to allow for such factors as the uneven dose distribution in the skeleton and the time of exposure. In an attempt to account for the duration of exposure, Evans et al. (1,2)

*See reference 1 for definitions of these quantities.
**This dose classification has been altered by Evans et al. (2) from that given by Evans et al. (1), in which a class f included a range of 1000 to 1200 CR and class 1 included a range from 1200 to 2500 CR.
***For discussion of this concept, see reference 1.

have introduced the CR and CRY concepts. The limitations of these dose estimates, however, require emphasis. For simplicity, only the CR will be discussed since similar limitations apply to the CRY as well.

The calculation of CR from current or terminal burden measurements, which are reported as Pure Radium Equivalents (PRE)*, depends on the assumption of a retention function for both radium and radon in the human (18). Several radium retention functions and one radon retention function have been previously mentioned. With this information, it is possible to calculate the effect of different radium retention functions on cumulative rads.

For example, consider an individual with a 1 μCi residual burden of ^{226}Ra after 40 years. The computational details of the CR for different radium retention functions are given in Appendix I and the results are shown in Table 1. A 7 kg skeleton was assumed for all CR calculations, and an ingestion period of one year (365 days) was assumed for calculations which included Eq. (2).

Table 1
MAXIMUM BURDEN AND CR BY DIFFERENT RADIUM RETENTION MODELS

Equations[a]	Parameters (a and b)	Maximum Burden Estimate (μCi)	Cumulative Rads (CR)
1	Norris et al. (16) (a = 0.54, b = -0.52)	271	2307
1	Miller and A. Finkel (17) (a = 0.30, b = -0.44)	227	1957
2	Norris et al. (16) (a = 0.54, b = -0.52)	14	2199
2	Miller and A. Finkel (17) (a = 0.30, b = -0.44)	9	1892

[a]Equation 1. $R(t) = a\ t^b$, $t \geq 1$.

Equation 2. $R(t) = \frac{a}{b+1}((t + 365)^{b+1} - t^{b+1})$, $t \geq 0$.

*For discussion of this concept, see reference 1.

Note in Table 1 that the maximum burden and cumulative rad estimates are dependent upon choice of retention function* and that the dose estimates corresponding to the other models are less than the estimate resulting from the model which Evans et al. (1,2) assume. The CRY estimates are affected in a similar manner.

This dependence of CR and CRY on the choice of radium retention function, coupled with the recognized inhomogeneous distribution of radium in the skeleton, indicates that these dose estimates should not be mistaken as absolute absorbed doses. They should be kept in context as calculated dose estimates relative to an assumed radium retention function.

Second a difficulty arises in the testing of hypotheses. The test of the hypothesis that tumor incidence above 1000 CR is independent of dose, employed by Evans et al. (1,2), indicated a non-significant chi-square value. Thus the data can be said to agree with the hypothesis in the sense that they do not refute it, but this is not equivalent to acceptance. As Evans et al. (1) note, the weakness of accepting a tested hypothesis on this basis is due to the inability to precisely calculate the probability of error in accepting the tested hypothesis when it is false.

A third consideration treated by Evans et al. (1,2) is that of a "practical threshold." The definition of a "practical threshold" is given by Evans et al. (1) as the dose region "where the tumor appearance time exceeds the life-span" of the individual. The determination of a numerical value for the practical threshold appears to be based on the extrapolated lower tumor appearance distribution envelope (Figure 9 of Evans et al. (1)) which connects three extreme points of the plot of tumor appearance time against rads (CR). The contrast between their method and an extrapolated least squares (LS) line, fit to the data**, is shown in Figure 1.

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*Maletskos et al. (19) give a function describing the retention of ^{224}Ra for the first 20 days after injection. Calculations using this retention function for the first 20 days and Eq. (1) for beyond 20 days changed the CR by approximately 1% of the values obtained from the use of the power function alone 40 years after initial burden. This was true regardless of the set of a and b used in Eq. (1).

**This set of data includes all the studied tumor cases to date. The discovery of new data may alter the LS line, but at the present time it appears to fit the given data well.

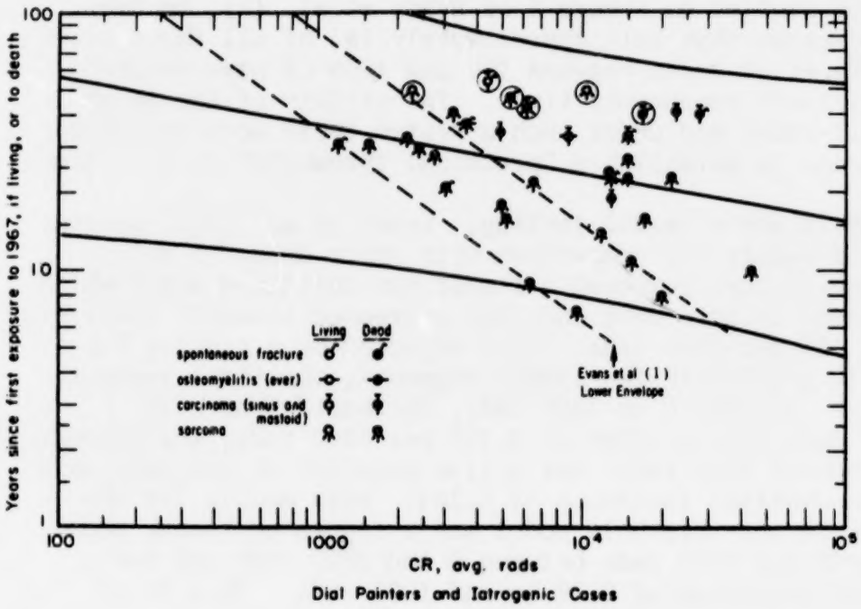

Figure 1 - Comparison of Tumor Appearance Times
[Reproduced from Figure 9 of Evans et al. (1)]

The value on the LS line is the average tumor appearance time for a given dose (CR) and the 95% confidence envelope involves the confidence limits about that average for a predicted value*. Values corresponding to Figure 1 are given in Table 2.

Table 2
COMPARISON OF TUMOR APPEARANCE TIMES

Dose (CR)	Evans et al. (Lower Limit) (Years)	Least Squares Line and Confidence Interval		
		Average (Years)	Lower 95% Limit (Years)	Upper 95% Limit (Years)
700	45	39	11.6	128
620	50	40	11.8	134
500	60	41	12.0	141
400	70	43	12.2	151
250	100	47	12.7	173
100	200	56	13.4	232

*For complete treatment of this concept see Chapter 9, reference 20.

The LS line, if plotted on Figure 5 of Evans et al. (1), becomes non-linear and indicates that only approximately 16% of all those cases still living who received doses between 100 and 1000 CR have reached or passed their LS tumor appearance times. The utility of the least squares fit is well-known and under such a system there does not appear to be strong evidence to establish a "practical threshold" at this time.

A fourth point is one of model testing. Evans et al. (1,2) present three non-threshold models for comparison with their data. A chi-square test of significance rejected a linear non-threshold model which indicated zero tumors at zero dose and then increased linearly from zero with a slope of 0.033 per 1000 rads. Also rejected by a similar test was a non-threshold model with two linear segments; the first segment, defined on the dose interval 0 to 1000 rads, increased from zero incidence at zero dose with a slope of 0.164 per 1000 rads; the second segment, defined beyond 1000 rads, was a line parallel to the dose axis corresponding to a constant incidence of 0.164. Both models fit the data poorly. A third non-threshold model was a segmented linear model with a slope of 0.29 per 1000 rads between 0 and 1000 rads and had a zero slope constant incidence of 0.29 beyond 1000 rads. This third model was not formally subjected to a test procedure and was thus not rejected. The authors applied probability calculations which attempted to indicate inconsistency of the data with this third model.

Finally, there is the consideration of variability of estimation. The finding by Evans et al. (1,2) that no tumors have been observed below 1100 CR (2) (recalculated to reflect the dose at diagnosis from 1200 CR (1) which is the dose at death) has obvious public health implications, especially with regard to a possible threshold for radium toxicity. The importance of this lowest dose for which a tumor has been seen would seemingly require some type of accompanying variability statement such as confidence limits. It has already been shown that the model dependence of CR could alter the numerical value but there are other considerations also. The residual burden measurements involve whole body counting using either the meter-arc or chair positions with their inherent variability. The a and b values in the retention functions determined by Norris et al. (16) are averages for which the associated standard errors have been determined. These measurement and retention model uncertainties warrant a variability statement so that the precision of the calculated estimate can be established.

In summary, the MIT data are not inconsistent with a hypothesis that the incidence is independent of the calculated dose above the dose estimate of 1000 rads. Though no tumors have been observed below 1100 rads (2), there is not sufficient evidence at this time to demonstrate a practical threshold. Three non-threshold models chosen by the authors appear to be inconsistent with the data. One of the three was a linear, non-threshold model. The rejection of these three models

does not imply a rejection of all non-threshold models. If one considers the uncertainties of dose estimation and variability, it would seem that the results of the MIT study are inconclusive at this time with respect to establishing a quantitative dose-response relationship, especially in the low dose range.

The ANL-ACRH Study

The ANL-ACRH series reported by A. Finkel et al. (3,4) is a group of radium dial painters, iatrogenic patients, and radium chemists from the Chicago, Illinois area. The burdens delivered to these individuals were, with two exceptions, always ^{226}Ra. Several retention models were determined on many individuals and, where possible, the retention functions were used to calculate a maximum burden from the measured residuals. Several radiation induced disease conditions were observed including bone sarcomas; carcinomas of the paranasal sinuses and mastoids; and leukemias and blood dyscrasias. For incidence calculations these disease conditions are summed together to get a total tumor incidence.

From an epidemiologic standpoint, several deficiencies exist in this study. The source of the population is not well defined and it is unclear what selection biases might be entering the stated incidence figures. Many of the cases included may be self-selected as A. Finkel et al. (3,4) recognize. This might bias the incidence figures to higher values than would ordinarily have resulted. Residual or terminal burden measurements were made for many reported cases, but for some the dates over which the burden was obtained were not known so no maximum burdens could be calculated. This absence of data is important because seven of these individuals had tumors and their loss to the incidence calculations necessarily affects the conclusions that are drawn.

A. Finkel et al. (3,4) give a good deal of consideration to retention function derivations. Their models have already been mentioned and they do indicate that variability is involved in their retention function determinations. They present tables (12(3) and VI(4)) in which the range of estimated maximum radium burdens is compared for several retention functions, parameter estimates, and type of diagnosis. For example, consider the ingestion function (Eq. 2) applied to patients with "osteo- and other sarcomas probably arising in skeletal tissues". Use of the average estimated parameters ($a = 0.30$, $b = -0.44$) gives a maximum calculated burden of 6.72 μCi, while the smallest ($a = 0.18$, $b = -0.22$) and the largest ($a = 0,89$, $b = -0.63$) estimates of the parameters give calculated maximum burdens of 2.28 and 17.35 μCi, respectively. By comparison, the maximum burdens calculated with the A. Finkel et al. (3,4) models are smaller than those of other investigators as has already been stated in Table 1.

There is only one inference type statement rendered by A. Finkel et al. (3,4). Based on the lowest maximum burden at which a tumor was observed, it indicates that the maximum permissible body burden of radium (0.1 μCi) is 12 times conservative. Since this case (03-685 ANL) has been reclassified (4)*, the 12 times no longer applies. However the variability in the maximum burden calculations, inherent in the retention function determinations, indicate that the stated maximum burden estimate given at 1.23 μCi could be as low as 0.42 or as high as 3.58 (3).

In summary, ANL-ACRH study emphasizes retention function determination. Missing bits of data and the possibility of inadvertant bias in data collection weaken the dose-response relationships and the incidence computations. Important questions have been raised concerning dose calculations from measured burdens. The illustration of several retention function estimates of maximum body burden combined with retention model variability indicate the need for caution in the interpretation of dose-response data in the human radium studies.

The Gofman and Tamplin Analysis

Further treatment of the human data has been given by Gofman and Tamplin (5,6). Using the Evans et al. (1) and Evans (22,23) data, Gofman and Tamplin (5,6) attempt to disprove the threshold hypothesis. Their assumption of a linear, non-threshold hypothesis is similar to that made by such groups as the ICRP, NCRP, and FRC in their deliberations of standard setting guidelines for some time. The second of the Gofman and Tamplin (5,6) assumptions, a doubling dose concept for all forms of cancer, is not so readily accepted. Nowhere in either human or animal studies is there any indication to support the assumption that radiation will increase every kind of tumor which arises spontaneously in a given population of individuals. In fact there is considerable evidence to the contrary (24).

If, however, both of the Gofman and Tamplin (5,6) assumptions are allowed, their argument still fails to achieve its objective of disproving the threshold theory. To disprove any hypothesis statistically, a direct test of that hypothesis is required. Gofman and Tamplin (5,6) fail to employ a test of any model hypothesis and hence fail to reject any, despite their contentions to the contrary. If the proper test of the hypothesis suggested by Gofman and Tamplin (5,6) were applied, the resulting conclusions would be only that the data are not inconsistent with a linear, non-threshold model under their assumptions. This argument does not suffice to disprove a threshold hypothesis.

*Disagreement exists about the classification of this case. Very competent general pathologists classified it as a squamous cell carcinoma, Grade I, while equally competent specialists in oral pathology believed it to be a non-malignant tumor of primitive epithelial rests or as a benign reaction to chronic infection (21).

The Gofman and Tamplin (5,6) works are also hampered by various other deficiencies. First, they miscalculate the average age at first insult and the average age in 1967 by using Figure 5 of Evans et al. (1) which does not contain complete information on all 496 reported cases. From the cases shown in Figure 5 (1), Gofman and Tamplin (6) calculate the average time from first insult to 1967 to be 47 years, and the average age at first exposure to be 26 years. Figures 1 and 3 of Evans et al. (1) report all 496 cases by "age at first exposure" and "years since first exposure to 1967 or death," respectively. From those two figures the average age at first exposure and the average time since first exposure to 1967 can be estimated to be 20 and 44 years respectively. If combining these averages is valid, then the average age in 1967 is their sum, 64 years. Thus, the Gofman and Tamplin (6) analysis should have considered ages 20 to 64 years, which would result in lower natural incidence computations than the 26 to 73 interval they used.

Second, the latent periods utilized by Gofman and Tamplin (6) are not representative of the MIT data. In Table 3, their latency periods are compared with those given by the lower envelope line of Evans, et al. (1) and our least squares line fit to Evans data as shown in Figure 1.

The use of the shorter latent period estimates would bias the natural incidence calculations upward because there are more years from the expiration of latency to 1967 than if the larger estimates are used and thus more tumors would be expected.

Table 3
LATENT PERIOD COMPARISONS

Gofman and Tamplin (6)		Estimated from Figure 1[a]	
Dose Range (Rads)	Avg. Latency (Years)	Evans et al. (1) Lower Envelope (Years)	Least Squares Mean Value (Years)
0 - 100	25	200	56
100 - 1200	20	48	40
1200 - 2500	15	25	33
>2500	10	10	27

[a]Values are rough approximations taken from the lines in Figure 1. For the first dose range (0-100 rads), the latent period estimates are for 100 rads as this is the lowest dose in the graph. For the middle two dose ranges, the arithmetic mid-range (650 and 1850 CR) are used to estimate latency. For the final dose range (>2500 CR), 5000 CR was arbitrarily chosen as the mid-range for estimating latency.

Third, the use of expected numbers as probabilities by Gofman and Tamplin (5,6) is not valid. Expected numbers by their nature can assume any value between zero and the total number at risk. Since the total number at risk is greater than unity, the expected number violates a basic law of probability, i.e., the probability is a number which has a lower limit of zero and an upper limit of one. Therefore it is incorrect to assume, as Gofman and Tamplin (6) do, that for an expected number of tumors less than one, the probability of no tumors is one minus the expected number. Obviously for an expected number greater than one this relationship cannot hold. The difficulty apparently arises from their failure to recognize the difference between the expected number of cases and the expected value of a discrete random variable.

These points substantially reduce the effectiveness of the Gofman and Tamplin (5,6) arguments.

Human Data Summary

Human radium data are limited. No one study appears large enough or sufficiently complete to resolve the non-threshold versus threshold controversy. Attempts are being made to combine the New Jersey dial painters, the MIT series, and the ANL-ACRH series (2)*. A dose-response relationship established using the combined study would apply only to a population which is predominantly female and which acquired a radium burden in the teens or early twenties. These findings would, however, be an important advance in the field of human radiobiology. In addition, every effort should be made to relate the work involving the toxicity of ^{224}Ra to the studies involving the toxicity of ^{226}Ra and ^{228}Ra in order to augment and to complete the present history of the human exposure to the radioisotopes of radium.

Furthermore, this review of the human radium experience deals with studies in which bone sarcomas and carcinomas of the paranasal sinuses and mastoids are the primary endpoints. Various other disease conditions appear in these studies for which a radium etiology can neither be established nor denied at this time, primarily because they have not been studied. For example, four central nervous system tumors have been observed in the ANL-ACRH series (25) and two have been seen in the MIT group (18,26). Numerous spontaneous fractures resulting from varying

*The first results of this effort were recently presented at the Research Conference on the Estimation of Low Level Radiation Effects in Human Population, Argonne National Laboratory, December 7-9, 1970, by R. E. Rowland, Patricia M. Failla, A. T. Keane, and A. F. Stehney in a paper entitled "Some Dose-Response Relationships for Tumor Incidence in Radium Patients." That paper was received too late for inclusion in this review.

degrees of radium deposition in the skeleton are evident in both the MIT (1,2,22,23) and ANL-ACRH (25) case histories. These and other effects such as life-shortening, leukemia, mammary gland tumors, and various other soft tissue tumors, which may be caused by radium, have definite public health implications; their investigation is necessary to complete the picture of human radium toxicity.

ANIMAL RADIUM STUDIES

Introduction

Animal experiments prior to 1944 (27-42) provide limited useful data. For the purpose of analysis the number of animals is too small (1 to 13), the dose too high (up to 4 mCi), and the animals were sacrificed too soon. If a large number of animals was used, either the exposure was percutaneous, the dose was unknown, the dose was mixed ^{226}Ra-^{228}Ra (MsTh), or the dose was used as an implant rather than ingested or injected (Table 4).

Three large studies with animals, two with large mammals and one with rodents, are discussed in this report. The two major large mammal experiments concerned with the long-term biological effects of internal emitters are those of the Radiobiology Division, Department of Anatomy, University of Utah (8,9) and the Radiobiology Laboratory, University of California at Davis (10). Both laboratories utilize the beagle dog as their experimental animal because it has a longer life span and a closer relationship to humans in matters of bone metabolism, physiology, and pathology than does the laboratory rodent. The rodent study, involving long-term effects of ^{226}Ra in mice, was conducted at Argonne National Laboratory (11).

The Utah Study

The Utah experiment (8,9), initiated in the early 1950's was designed to compare the effects of ^{239}Pu and ^{226}Ra. Substudies with ^{228}Ra and ^{228}Th were included to attempt to clarify the human radium poisoning data. A single intravenous injection of the radionuclide at approximately 18 months of age (adult) was administered at dose levels which are multiples of the maximum permissible level for ^{226}Ra in man.

The single injected radium animals, termed the Toxicity Animals, were maintained until death and the results are given in Table 5. Additional groups of radium dogs were studied as Test Animals which could be sacrificed as needed and the results of those groups appear in Table 6. Some of the Test Animals received the ^{226}Ra in six injections at 56-day intervals instead of a single injection; the dosage levels were similar to those of the Toxicity Animals.

TABLE 4
EXPERIMENTAL INDUCTION OF NEOPLASMS WITH RADIUM [a]

Author	Date	Substance	Quantity, mg of Ra	Species	No. of animals		Tumor Induc Time, Months	Type of Tumor
					Used	With Tumors		
Lazarus-Barlow	1918	Ra	10^{-4}-10^{-8}	Mouse	193	5	6	Carcinoma of skin
		Ra	10^{-3}-10^{-7}	Rat	53	?	?	
Daels and Baeten	1925-1926	Ra	10^{-6}-$6x10^{-3}$	Mouse	78	3	7-12	Sarcoma, spindle celled subcut.
				Rat	43	2		
Daels and Biltris	1931	Ra	Undeterminable	Rat	82	4	8-22)	Sarcoma of cranium,kidney,spleen
	1931-1933	Ra	.....	Guinea pig	100	18	8-22)	
	1937	Ra	.....	Chicken	152	2	58-59	Carcinoma of biliary tract, osteosarcoma
Schurch and Uehlinger	1931	Ra	10^{-4}-$5x10^{-3}$	Rabbit	1	1	18)	Sarcoma of bone, liver, spleen
Uehlinger and Schurch	1935-1938	Ra,Ms-Th 1	.....	Rabbit	56	18	18-50)	
Sabin et al.....	1932	Ra,Ms-Th 1	5.1 mg Ra 7.7 mg Ms-Th 1	Rabbit	7	2	11-19	Osteosarcoma
			$4x10^{-4}$-$1.8x10^{-3}$	Guinea pig	12	2	34-39	Carcinoma of biliary tract
							)	Carcinoma of skin
Ross	1936	Ra	0.1	Rabbit	13	6	24-32)	Fibro- and osteosarcoma
Jentzer	1937	Ra	0.5	Rabbit	6	1	9	Osteosarcoma
Hellner	1938	Ra	.....	Rabbit	...	..	24	Sarcoma, polymorphous
Dunlap et al.....	1944	Ra	$2x10^{-6}$	Rat	13	9	12	Osteosarcoma

[a] Modified from Lacassagne, Antoine (1945) by Hollaender, A., Ed. Radiation Biology, VOL I, Part II, McGraw-Hill Book Company, Inc., N.Y. 1954, p.1155.

TABLE 5

UNIVERSITY OF UTAH
^{226}Ra
TOXICITY ANIMALS

Treatment Level Code[a]	Dose, μCi/Kg	No. of Dogs	Deaths	Deaths with Osteosarcoma	Osteosarcoma	
					Av. Yrs. Injection to Death	Av. Rad Dose One Yr. Before Death
R5	10.4	10	10[b]	9	3.04	10900
R4	3.21	13	13[c]	12	4.36	4530
R3	1.07	12	12[d]	11	6.28	1940
R2	0.339	13	13	5	10.28	837
R1.7	0.166	12	9	1	11.25	458
R1	0.0621	23	12	0		
R0	0.0000	40	12	0		

[a]Recently introduced levels in this experiment in which no deaths have occurred to date:
R0.5 = 0.0220 μCi/kg
R0.2 = 0.0074 μCi/kg
[b]One distemper death at 481 days (1.31 yrs.)
[c]One distemper death at 490 days (1.34 yrs.)
[d]One pyometritis death at 1610 days (4.41 yrs.)

TABLE 6
UNIVERSITY OF UTAH
^{226}Ra
TEST ANIMALS (OTHER THAN SACRIFICE[a])

Treatment Level Code	No. of Dogs	Deaths with Osteosarcoma	Osteosarcoma		Other Deaths
			Av. Yrs. Injection to Death	Av. Rad Dose to Death	
R5	12	6	3.36	10832	3 Nephritis 1 Melanoma 1 Crippling fracture 1 Strongyloides infection
R4	9	9	4.23	4262	
R3	5	4	5.15	1605	1 Still living

[a]Not included are many of these test animals which were sacrificed for metabolism distribution, retention, and other special studies.

All of the animals in the four highest radium dose levels (R5, R4, R3, and R2 of Table 5) are now dead. Only one death in each of the three highest levels was not caused by osteosarcoma, and in each of those three cases death occurred prior to the onset of the osteosarcoma deaths. At the fourth highest level (R2), 5 of 13 dogs have died from osteosarcoma, 7 have died from other causes, one of which is believed by the authors (8,9) to be radiation related (a carcinoma of the tympanic bulla), and the cause of death in one animal is undiagnosed. At the fifth highest level (R1.7 which is 3 times level 1), one death has been attributed to an osteosarcoma and eight from other non-radiation related causes. In the next lower dose level (R1), none of the 12 deaths are considered by the authors (8,9) to have been influenced by radiation. In the control group (R0), 12 of the 40 animals have died but none with spontaneous tumors similar to those which had been produced in the irradiated groups.

No deaths have been reported in the two lowest dose level groups (R 0.5 and R 0.2) but they have not been operational for sufficient duration for deaths to occur. In the Test Animal groups at Utah (8,9), osteosarcomas have occurred in the three highest dose levels with times from injection to death that are comparable to those for osteosarcoma at similar dose levels in the Toxicity experiment (Table 6).

The Davis Study

The University of California at Davis study (10) originated in the middle 1950's to evaluate the relative toxicity of ^{90}Sr and ^{226}Ra in the beagle dog. The dosage levels of ^{226}Ra paralleled those of the Utah study (8,9), but the isotope was given in eight equal semi-monthly injections beginning at 435 days of age (Table 7) rather than the single injection method of the Utah experiment (8,9). It was estimated that this four month injection period in the dogs paralleled the three year "brief exposure" periods during which most of the human subjects had received their radium burdens, whether injected or ingested.

The Davis study (10) is incomplete at the present time but some preliminary results have been obtained. Fifteen osteosarcoma deaths have been reported thus far with nine occurring in the highest level (R50) and six in the next highest level (R40), (Table 7). There are no reports on deaths other than osteosarcoma, if any have occurred, in any of the radium injection levels.

The Argonne Study

In a large experiment at the Argonne National Laboratory, M. Finkel et al. (11) used over 3200 CF1/ANL mice to determine the long-term effects of single intravenous injections of ^{226}Ra. Female mice

TABLE 7

UNIVERSITY OF CALIFORNIA (Davis)

^{226}Ra INJECTION SERIES

Treatment Level Code	No. of Dogs	μCi/kg/injected[a]	Osteosarcomas	Injection to Death, (Years)
R50	38	1.25	9	4.4
R40	41	0.42	6	4.9
R30	39	0.14	0	
R20	41	0.047	0	
R10	38	0.008	0	
R05	46	0.003	0	
R00	81	0.000	0	

[a]8 semi-monthly IV injections starting at 435 days of age.

seventy days old were divided into 14 dose levels ranging from 0.05 to 120 μCi/kg. These administered amounts produced retained burdens that were 5 to 12,000 times the maximum permissible body burden (MPBB) for humans (Table 8). The most sensitive indicator of radium damage was osteosarcoma which appeared at dose levels where other histological types of radiation damage were not apparent (Table 9).

Average tumor expectancy (11), the number of osteosarcomas still to appear divided by the number of animals still alive, was calculated for each dose level. These values plotted as a function of amount of radium injected increased in a linear fashion from the control value to the 2.5 μCi/kg level (Fig. 2). At 2.5 μCi/kg and again at 20 μCi/kg the dose response curve changed direction abruptly which in the opinion of the authors (11) reflected severe lethal damage at the high dose level and the possible existence of several mechanisms of oncogenesis of changing importance at the lower level.

The merits of the average tumor expectancy, similar to life expectancy, are difficult to judge in a dose-response context. The implications of more than one tumor expected per animal on a binomial incidence variable are not clear and comparison between this dose-response relationship and those given by others is virtually impossible without a common response indicator. The resulting linear relationship is transformed to a non-threshold, curvilinear, concave down function if the response variable is changed to tumor incidence.

On the basis of the linear response shown between tumor expectancy and increasing levels of radium, some estimates of tumor expectancy at the MPC allowed in man were made by M. Finkel et al. (11). These estimates indicated that at 0.0014 μCi/kg (equivalent to 0.1 μCi in a 70 kg man) the tumor expectancy would be 1.3 times that of the controls. If, however, the tumor expectancy was calculated for this level as a retained dose (14% at 200 days), the osteosarcoma expectancy would be 3.85 times that of the controls.

Animal Data Summary

In summary, of the large studies using bone seeking radioisotopes, the U. of California (Davis) study (10) has not been operational long enough to produce meaningful amounts of dose-response data. Although some osteosarcomas have appeared at the highest levels, none of the groups has lived out its lifespan to date.

The study at Utah (8,9) has sufficient duration that some groups have completed their lifespans, but additional animals have been added to some groups (R1 and R0) and two new groups have been added (R 0.5 and R 0.2). Since there is 100% incidence of osteosarcoma at the two highest dose levels, a curve of almost any shape can be drawn through the points representing incidence at the three remaining dose levels.

TABLE 8

RADIUM TOXICITY STUDIES
COMPARISON OF DOSE LEVELS

Retained Dose (MPBB)[a]	DAVIS (Dogs)	UTAH (Dogs)	ARGONNE (Mice)
12,000	-	-	A
8,000	-	-	B
4,000	-	-	C
2,000	-	-	D
1,620	R50	R5.0	-
1,000	-	-	E
540	R40	R4.0	-
500	-	-	F
250	-	-	G
180	R30	R3.0	-
125	-	-	H
100	-	-	I
75	-	-	J
60	R20	R2.0	-
50	-	-	K & M
30	-	R1.7	-
25	-	-	N
10	R10	R1.0	O
5	-	-	P
3.3	R05	R0.5	-
1.1	-	R0.2	-
0	R00	R0.0	L & R

[a]Retained dose is shown as multiples of the Maximum Permissible Body Burden (MPBB), which is defined as 0.1 μCi ^{226}Ra per 70 Kg man for radium workers.

TABLE 9

SUMMARY OF OSTEOSARCOMA DATA[a]

Group	Amount Injected (μCi/kg)	Number of Mice	Mice with Osteosarcoma (%)	Average Number per Mouse	Average Osteosarcoma Expectancy
A	120.0	45	31.1	0.467	1.011
B	80.0	45	68.9	1.330	1.880
C	40.0	45	73.5	1.360	1.724
D	20.0	45	84.5	1.400	1.721
E	10.0	45	75.5	1.000	1.250
F	5.0	45	62.3	0.956	.980
G	2.5	105	42.8	0.600	.851
H	1.25	105	21.0	0.305	.405
I	1.0	240	23.4	0.317	.377
J	0.75	510	18.5	0.208	.267
K	0.50	600			
M	0.50	90			
		690	11.6	0.143	.195
N	0.25	255	7.45	0.078	.081
O	0.10	255	1.96	0.020	.058
P	0.05	255	4.32	0.043	.077
L	0.0	420			
R	0.0	105			
		525	1.14	0.011	.014

[a]Modified from Finkel, M. P., Biskis, B. O., Jinkins, P. B., (1969) Toxicity of Radium-226 in Mice. In Radiation-Induced Cancer, International Atomic Energy Agency, Vienna, pp 369-391.

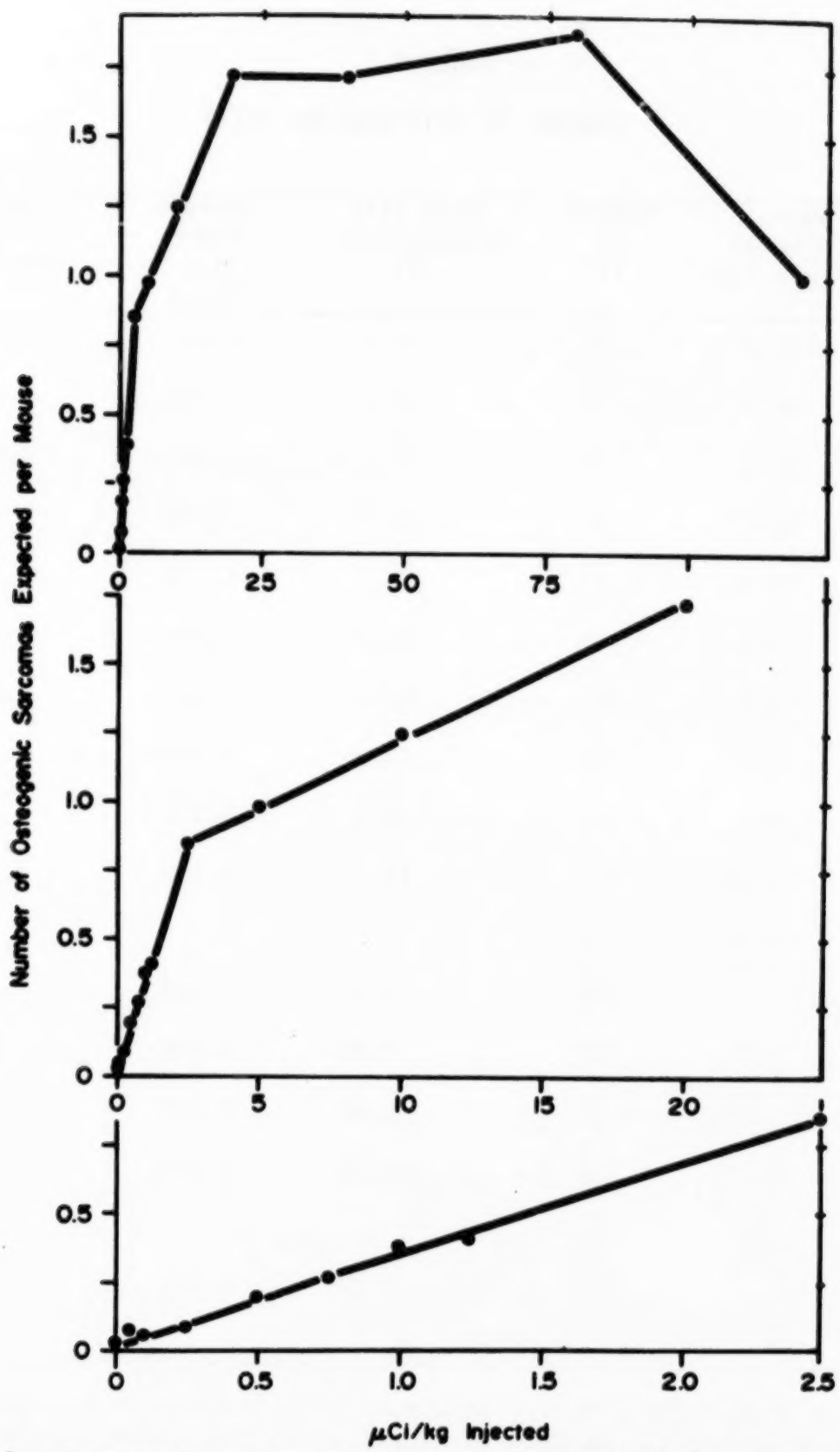

Figure 2. Average tumor expectancy as a function of the amount of radium injected. (Reproduced from Fig. 7 of M. P. Finkel et al.(11)).

M. Finkel et al. (11) have reported a dose-response curve for ^{226}Ra with three linear segments for CF1/ANL mice. The first segment rose from zero in steep manner; the second segment was more flattened; and the final segment was a plateau ending at the dose beyond which death from radium toxicity preceded osteosarcoma development.

In an effort to correlate the animal and human radium data, an increased scope in the animal studies may be needed. In the animal studies discussed here, only bone sarcomas were considered*. In the light of other malignancies found in the human studies which may have a possible radium etiology, the investigation of these effects in animals would be very useful in trying to confirm or deny radium as the cause.

CONCLUSIONS AND RECOMMENDATIONS

In evaluating the information reviewed in this report, distinction must be made between dose-response models which attempt to describe radiation effects as accurately as available information permits, and public health protection standards which, recognizing that the real health effects of radiation are incompletely known, make allowance for margins of safety that are considered to be reasonable and prudent. From this standpoint, there is no reason for conflict between the two philosophies or between the different models associated with these philosophies. Only when a protection standard model is assumed to be the dose-response model or vice versa does conflict occur.

The review of the human data covered in this critique is based on two studies. The ANL-ACRH study (3,4) lacks sufficient information to support a dose-response model. Evans et al. (1,2) hypothesize the existence of a practical threshold. Uncertainties in the metabolic model used for dose estimate calculations and deficiencies in the extrapolation procedure make acceptance of that hypothesis unwarranted. The Gofman and Tamplin (5,6) analysis of the MIT data appears inadequate for the conclusions they have reached.

The animal radium data review was based on three studies, two of which (the Utah (8,9) and Davis (10) studies) are still in progress and as yet inconclusive. The mouse study (11) indicates a non-threshold model which was linear over selected dose ranges. When tumor incidence is used as the response indicator for the mouse study (11), a non-threshold curvilinear concave down function results.

*The most recent report from the University of Utah study (Work in Progress in the Internal Irradiation Program, C00-119-242, 1970) presents evidence to support classification of certain intraocular melanomas in beagles as being radiation induced. The import of this finding is that two of these intraocular tumors were observed in the R1.0 dose level which is about one third as great as the lowest dose level (R1.7) in which osteosarcomas have been observed.

Based on these five studies, there does not appear to be sufficient data to establish whether or not there is a threshold for radium toxicity at low levels of body burden. Any conclusion concerning a dose-response model based on these data is probably premature. Further experimentation will probably be required before a dose-response function of ^{226}Ra can adequately be determined.

A number of factors were not included in the final development of this staff analysis. In part, this is due to the difficulties inherent in estimating the impact of certain parameters of radiological health importance. Thus, the effects of dose rate, dose distribution, diet, age, wasted radiation, etc., on the determination of dose-response models is not discussed. Considerably more study using experimental techniques will, in all probability, be required before these and other factors can be allowed for in the development of dose-effect response curves.

In the opinion of this task group, public health authorities should continue to follow the philosophy adopted by ICRP, NCRP and FRC of a linear, non-threshold model (44) for recommending acceptable limits of human radiation exposure to radium and to other radionuclides whose standards are based on that of radium. This recommendation does not imply that proof of the linear, non-threshold model has been demonstrated, nor does it constitute a rejection of the possible existence of a threshold. It is merely the most cautious and reasonable approach to assume that any radiation exposure has an accompanying biological risk in the absence of any proof to the contrary.

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Appendix I

Dose Estimate Calculations

Evans et al. (18) give the equations for determination of CR by

$$CR(T) = \int_0^T R(t)\, dt$$

and

$$R(t) = Q_1 F_{Ra}(t) + Q_2 F_{Rn}(t) + Q_3 F_{RaF}(t)$$

where CR(T) are the cumulative rads after time T from cessation of administration; R(t) is the dose rate function in rads per unit time at time t after administration; $F_{Ra}(t)$, $F_{Rn}(t)$, and $F_{RaF}(t)$ are the retention functions of ^{226}Ra, ^{222}Rn, and RaF respectively; and Q_1, Q_2, and Q_3 are the energy constants changing microcuries to rads for ^{226}Ra, ^{222}Rn, and RaF respectively. The ^{226}Ra contribution to CR is simply the first term in the sum for R(t). So,

$$CR(T) = \int_0^T Q_1 F_{Ra}(t)\, dt$$

for radium only.

Norris et al. (16) give a method for determining maximum burden (equals amount injected) by altering Eq. (1) of text as follows

$$F_{Ra}(t) = aq\, t^b$$

where q is the initial injected amount of radium. The q value can be found for t days after administration by

$$q = \frac{F_{Ra}(t)\, t^{-b}}{a}$$

For Eq. (2) a similar value k can be incorporated as

$$F_{Ra}(t,F) = \frac{ak}{b+1}\left[(t+F)^{b+1} - t^{b+1}\right]$$

and solving for k gives the desired adjustment constant. These constants are necessary because Eq. (1) and Eq. (2) are valid for 1 μCi initial burden.

The Q-values have been determined by Evans et al. (18) and for radium alone $Q_1 = 0.0348$, assuming a standard male skeleton. The general integrals for CR are given for Eq. (1) and Eq. (2) respectively below:

$$CR_1\ (T) = Q_1 \int_0^T F_1 Ra(t)\ dt$$

$$= 0.0348 \int_0^1 q(A_0 + A_1 t + A_2 t^2)\ dt^* + \int_1^T aqt^b\ dt$$

$$= 0.0348\ q\left[A_0 t + A_1 \frac{t^2}{2} + A_2 \frac{t^3}{3}\right]_0^1 + q\left[\frac{a}{b+1}\ t^{b+1}\right]_1^T$$

$$= 0.0348q\left[A_0 + \frac{A_1}{2} + \frac{A_2}{3} + \frac{aT^{b+1}}{b+1} - \frac{a}{b+1}\right] \qquad (3)$$

and

$$CR_2\ (T) = Q_1 \int_0^T F_2 Ra(t)\ dt$$

$$= 0.0348 \int_0^T \frac{ak}{b+1}\left[(t+F)^{b+1} - t^{b+1}\right]dt$$

$$= \frac{0.0348\ ak}{b+1}\left[\frac{(t+F)^{b+2}}{b+2} - \frac{t^{b+2}}{b+2}\right]_0^T$$

$$= \frac{0.0348\ ak}{(b+1)(b+2)}\left[(T+F)^{b+2} - T^{b+2} - F^{b+2}\right] \qquad (4)$$

Substituting the proper constants into Eq. (3) and Eq. (4), one obtains the doses due to radium alone where T and F are in days and a 7 kg skeleton is assumed.

To compute the total cumulative rads due to radium and all of its daughters, one must get the ^{222}Rn and RaF contributions. Since the ^{222}Rn retention function is similar for several species, including man (43), we shall assume that ^{222}Rn retention is characterized by the Norris et al. (16) function for radon (Eq. (1)

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*Since $F_{Ra}(t) = aqt^b$ is not valid below t = 1, a quadratic is assumed and constants are determined by Evans et al. (18).

with a = 0.021 and b = -0.28)*. Evans et al. (18) give the total CR for a 1 μCi initial burden as 8.51 CR after 40 years. Since the contributions of each of the α-emitters are additive, one can compute the contribution of the daughters after 40 years by subtracting from 8.51 CR the contribution due to radium alone under the Evans' et al. (18) assumptions. Substituting in Eq. (3) with q = 1, a = 0.54, b = -0.52, A_0 = 1, A_1 = 0.1792, and A_2 = -0.6392, one obtains the value of 3.898 CR for radium alone. By subtraction, one calculates the contribution of the daughters of radium to be 4.612 CR for 1 μCi initial burden of radium. Therefore, the contribution of the daughters, given an initial radium burden of q μCi, is the product, Q(4.612 CR).

Total CR calculations involving the power function of Eq. (1) for radium are the sum of the result from Eq. (3) with 4.612 q' where q' is the maximum burden corresponding to the a and b used in Eq. (3). The computations of total cumulative rads using Eq. (2) involve the sum of the result from Eq. (4) with 4.612 q', where q' is the maximum burden from the single injection model from which the a and b are obtained for use in Eq. (2) and Eq. (4). The use of the single injection maximum burden to calculate the contribution of the radium daughters while using the ingestion model for the radium contribution biases the total CR computation, involving the latter model, upward slightly. The reason for the bias is that the power function is greater than the ingestion function for all values of t greater than one day but less than 14610 days (40 years). The difference between the models, however, becomes small (<1 μCi) at approximately one year (t = 365) after initial burden, and it was decided that the point being made would not be further enhanced by working out the complicated derivation of the exact expression for the contribution to CR due to the radium daughters.

*Computations with values given by Miller and A. Finkel (17) result in a power retention function for radon (Eq. (1)) with a = 0.017 and b = -0.26 which are very close to the values given by Norris et al. (16).